Incidence, risk factors, survival and treatment of bone metastases from colorectal cancer

Systematic review

Christensen, Troels Dreier; Jensen, Sandra Galinska; Larsen, Finn Ole; Nielsen, Dorte Lisbet

Published in:
Journal of Bone Oncology

DOI:
10.1016/j.jbo.2018.09.009

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

Journal of Bone Oncology 13 (2018) 97–105

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Review Article

Systematic review: Incidence, risk factors, survival and treatment of bone metastases from colorectal cancer

Troels Dreier Christensen*, Sandra Galinska Jensen, Finn Ole Larsen, Dorte Lisbet Nielsen

Department of Oncology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev Ringvej 75, DK-2730 Herlev, Denmark

ARTICLE INFO

Keywords:
Colorectal cancer
Bone metastases
Incidence
Risk factors
Survival
Bisphosphonate treatment

ABSTRACT

Background: Bones are not considered a frequent metastatic site in patients with colorectal cancer (CRC). The purpose of the present study was to determine the incidence of bone metastases (BM) in CRC, to identify possible risk factors for BM, survival after BM, and effect of treatment of BM including antiresorptive treatment.
Material and methods: A computer-based literature search was carried out using PubMed and EMBASE.
Results: We included 29 studies. One randomized placebo controlled trial (RCT) study, two autopsy studies, five register studies, and twenty retrospective cohort studies. The studies described different cohorts making direct comparison difficult. Three studies analysed the effect of different treatments for BM including one RCT study.
Conclusion: The incidence of bone metastases was 3–7% in patients with CRC, and it was not possible to detect an increase in incidence over time. The most well established risk factors for BM are rectal cancer, having lymph node invasion at surgery of primary tumor, and lung metastases at any time. Other risk factors such as *RAS* mutation status have been suggested but results are not conclusive. Survival ranges from 5 to 21 months after diagnosis of BM depending on cohort, with survival of about 8 months in unselected patients. Several variables have been suggested as potential prognostic markers but are all poorly investigated. Treatment of BM is not well investigated, though patients seem to benefit from bisphosphonate treatment with regard to lower risk of skeletal related events. This review highlights the need for new research in the area.

1. Background

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with an estimated 1.4 million cases worldwide. In 2012 metastatic CRC (mCRC) was the cause of death in 693,900 patients [1], despite the advantages in screening, diagnosis and improved surgical and medical treatments.

About 20% of patients with CRC have already distant metastases at presentation [2] and totally 50% of patients with CRC will develop metastatic disease [3]. Moreover, a recent Norwegian study showed that 15.6% patients with CRC, who were considered surgically cured, had recurrent cancers including distant metastases during a five year follow up [4].

Today little is known about bone metastases (BM) from CRC. BM are considered frequent among patients with breast cancer, prostate cancer and lung cancer [5]. Bones are in fact the most frequent metastatic site among patients with breast cancer since up to 70% of all patients with disseminated breast cancer develop BM [6]. In breast, prostate and lung cancer, the antiresorptive treatment, bisphosphonates and denosumab, reduces further progression in bones and prevents complications by reducing the upregulated osteoclast activity caused by the metastasis. The outcome is fewer skeletal related events (SRE), and in the long term the antiresorptive treatment has an analgesic effect [7–10].

Since the relative survival of CRC has increased over the recent decades [11], we expect to see an increasing number of patients in our clinical practice with BM from CRC. For that reason, basic knowledge of the incidence, possible risk factors, survival and treatment of BM from CRC is essential, hence this review was made.

2. Method

In order to systematically review the literature about BM from CRC we completed the following search in PubMed on the 24th of September 2017 which resulted in 1064 hits: (((Bone AND metastases)) OR ("Neoplasm Metastasis"[Mesh] AND Bone)) OR (("Neoplasm Metastasis"[Mesh]) AND ("Bone and Bones"[Mesh]))) OR "bone metastases") OR "bone metastasis")) AND ((((("rectal cancer") OR "colon cancer") OR "colorectal cancer") OR "Colorectal Neoplasms"[Mesh]).

* Corresponding author.
E-mail addresses: troels.dreier.christensen.01@regionh.dk (T.D. Christensen), Sandragalinska@gmail.com (S.G. Jensen), finn.ole.larsen@regionh.dk (F.O. Larsen), dorte.nielsen.01@regionh.dk (D.L. Nielsen).

https://doi.org/10.1016/j.jbo.2018.09.009
Received 10 September 2018; Accepted 20 September 2018
Available online 22 September 2018

The following search was performed in EMBASE on 18th November 2017 resulting in 1374 hits: ((rectum cancer or rectum tumor or rectum carcinoma or colorectal cancer or colon carcinoma or colon tumor or colon cancer) and bone metastasis).

To ensure a complete search we also searched for “Metastatic pattern AND ((((("rectal cancer") OR "colon cancer") OR "colorectal cancer") OR "Colorectal Neoplasms"[Mesh])” in PubMed (1013 hits) and ((Rectum cancer or rectum tumor or rectum carcinoma or colorectal cancer or colon carcinoma or colon tumor or colon cancer) and metastatic pattern) in EMBASE (52 hits).

The searches were last updated 2nd July 2018.

Furthermore, we searched reference list of relevant studies.

We included human studies written in English describing patients with BM from CRC. The studies should include at least 10 patients with BM from CRC. Reviews, case stories and studies published before 1975 were excluded. In total 29 studies were identified through our search of the literature [12–40].

The following information was extracted; incidence of BM, survival after BM diagnosis, treatment of BM and follow-up. If the authors did not display the incidence, we calculated it by dividing the number of patients with BM with the number of patients with CRC.

Furthermore, results of any statistical analysis regarding risk factors for developing BM, risk factors for poor survival after BM, and treatment efficacy were extracted.

3. Results and discussion

We included 29 studies (Table 1). One study was a randomized placebo controlled trial (RCT) [40], two were autopsy studies [38,39], five were register studies [33–37]. Twenty-one were retrospective cohort studies [12–32]. Six studies included unselected cohorts of patients with CRC [12–15,33,34]. The remaining studies included various cohorts of patients, for example cohorts only including patients with mCRC, CRC patients who underwent surgery, patients with adenocarcinoma or only rectal cancer patients [1–32,35-40]. Furthermore, most studies did not report the exact follow-up period and those that did had different follow-up periods. This made a direct comparison across studies difficult and interpretation of results challenging.

3.1. Incidence of BM

Twenty-seven of the studies reported an incidence of BM among their patients. The incidence of BM among the various subpopulations of CRC patients is presented in Table 1.

The incidence of BM in unselected patients with CRC was described in three retrospective cohort studies [13–15] and two large register studies [33,34] and ranged from 2.9% to 6.6%. The distribution of stage and exact follow-up period in these studies were not accounted for. A sixth study followed all patients until death, but unfortunately, they did not provide an exact incidence. However, they stated that 264 patients among more than 2500 patients developed BM giving an incidence around 10% [12]. As expected a higher incidence of BM was generally found when only including patients with mCRC. Two cohort studies described an incidence of BM of 7% and 6.9% among these patients [26,27] and the register study by Riihimaki et al. reported an incidence of 9.3% [34] A fourth study presented an incidence of 10.4% in a population of patients with mCRC adenocarcinoma [28]. Most of the studies might have underestimated the true incidence. Firstly, most studies did not report the exact follow-up period, and only one study reported that they followed patients until death. Secondly, all studies were retrospective or register based and mostly based on routine follow-up schemes, which not necessarily would capture asymptomatic BM.

Two autopsy studies also presented an incidence of BM among patients with CRC ranging from 1.7% in a study by Hugen et al. [38] to 23% in a study by Katoh et al. [39]. However, in both studies there was a potential heavy selection bias since autopsies were not described as being performed on all patients but only after request from doctors or patients. Therefore, these results should be interpreted with caution.

It has been suggested that the incidence of BM from CRC is increasing due to better diagnostics options and CRC patients living longer, but so far this has remained as speculations. In this review we were not able to assess if the incidence varied over time, due to differences in patient populations and overlap in time periods for data collection in the included studies.

3.2. Risk factors for BM

Fifteen studies described a statistical analysis of potential risk factors for BM [12,15,16,18,19,22,25,28,30–32,34,35,38,39]. Summary of their results is presented in Table 2. All studies were retrospective and they described different cohorts making comparison of the results difficult.

3.2.1. Primary tumor location

From the studies included in this review it seems likely that location of primary tumor affects the likelihood of BM, with an increasing risk of BM the more distal the tumor is located.

Eight out of twelve studies that compared the risk of BM among rectal and colon cancer patients [16,19,22,25,28,30,34,35] identified an increased risk among patients with rectal cancer, and none of the four remaining reported the reverse association [12,32,38,39]. Five studies presented results of multivariable analysis and in all studies rectal cancer was identified as an independent risk factor for BM [15,16,19,22,34]. The OR for BM among patients with rectal cancer compared to colon cancer was on multivariable analysis 1.5 (CI 95% = 1.4–1.7) in a large register study by Riihimäki et al. [34], and between 2.0 and 2.4 in three retrospective cohort studies [15,19,22]. Sundermeyer et al. did only report p values from their multivariable analysis [28].

The specific location colon or rectum might also affect the risk of BM. A study by Chiang et al. which only included patients with rectal cancer, identified an increased incidence of BM in distal rectum (11.11%), compared to the middle rectum (6.95%) and in the proximal rectum (3.44%) ($p < 0.001$) [25]. A similar result among colon cancer patients was observed by Riihimäki et al. [34]. They identified an OR for developing BM of 1.2 (CI 95% = 1.1–1.4) for patients with distal colon cancer opposed to proximal cancer.

A potential bias of the result could be that direct invasion of the bone was included as bone metastases, none of the studies reported that they excluded direct invasion in their analysis. The pattern of metastases could be explained by Batson's venous plexus, a network of valveless veins that connect the deep pelvic and thoracic veins to the internal vertebral venous system [20,30,39,41].

3.2.2. Primary tumor stage

No firm conclusions can be made regarding potential association between primary tumor stage and risk of BM. A study by Sundemeyer et al. conducted on mCRC patients, found a significant association between incidence of BM and early stage cancer on multivariable analysis [28].

Oppositely, Sun et al. and Zhenghong et al. identified a significantly increasing incidence of BM with increasing stage in univariate but not multivariate analysis. Both also included patients with CRC who did not developed metastases, and therefore the association found on univariate analysis most likely reflects the increased risk of all metastases in higher stages [15,19]. Oppositely, two cohort studies found no association [12,16].

3.2.3. Histological type of CRC and mutation status

Results regarding primary tumor grade (well differentiated, moderately differentiated, poorly differentiated or undifferentiated) and

Table 1
Studies included.

AuthorYearCountry	Years	Patients	No. CRC	No. BM	Incidence of BM (%)	95% CI (%)	Survival after BM diagnosis	Follow up
Retrospective studies								
All cases diagnosed with CRC								
Santini et al. 2012 Italy [12]	1985-2009	All cases with CRC	>2500	264	~10	9.4 - 11.8	Median 7 months	NR – all dead at last follow up
Portales et al. 2015 France [13]	1996-2006	All cases with CRC	2434	110	4.5	3.7 – 5.4	Median 9.4 months	-
Bonnheim et al. 1986 USA [14]	1970-1980	All cases with CRC	1406	66	4.7	3.6 - 5.9	Median 7 months	-
Zhenghong et al. 2017 China [15]	2006-2015	All cases with CRC	2066	102	4.9	4.0 – 6.0	-	-
Selected patients with CRC								
Li et al. 2017 China [16]		Underwent radical surgery. $T_{any}N_{any}M_0$	1749	50	2.9	2.2 - 3.8	-	5 years
Baek et al 2016 South Korea [17]	2007-2013	Underwent surgery (including surgery for stage 4)	5479	63	1.2	0.9 - 1.5	Median: 17.8	Mean 19.6 months
Lan et al. 2015 Taiwan [18]	2000-2010	Underwent surgery (including surgery for stage 4)	1492	20[a]	1.3	0.9 - 0.21	-	Median 69.7 months
Sun et al. 2015 China [19]	2004-2009	Underwent radical surgery (including surgery for stage 4) Adenocarcinoma No BM at primary surgery	516	31	6.0	4.1 - 8.4	-	Median 69.5 months
Jimi et al. 2013 Japan [20]	1993-2008	Underwent surgery (including surgery for stage 4)	627	24	3.8	2.5 - 5.6	Median 6 months	-
Nozue et al. 2002 Japan [21]	Not reported	Underwent surgery (including surgery for stage 4)	928	12	1.3	1 - 2.2	Median 5 months	-
Liu et al. 2016 China [22]	2006-2014	Underwent surgery (including surgery for stage 4)	10,132	242	2.4	2.1 - 2.7	Median 15.6 months	Median 21.1 months
Roth et al. 2009 USA [23]	2000-2008	Only patients with CRC and a PET/CT	252	14	5.5	3.1 - 9.1	Mean 15.9 months	Mean 38 months
Amri et al. 2015 USA [24]	2004-2011	CC – patients with single segment resection**	974	-	Right colon: 1.4 Left colon: 0 Sigmoid: 1.9	-	-	Median Right colon: 42 months Left colon: 45 months Sigmoid: 45 months
Chiang et al. 2014 Taiwan [25]	2002-2006	RC; T3/T4 - underwent surgery M0; No preoperative radiation or chemotherapy	884	51	5.8	4.3 - 7.5	-	Mean 77.8 months
All cases with mCRC								
Patanaphan et al. 1993 USA [26]	1979-1982	mCRC	163	11	7	3.4 - 11.8	Median 10 months	-
Besbeas et al. 1977 USA [27]	1960-1970	mCRC	765	53	6.9	5.2 - 8.9	Mean 13.2 months	-
Selected patients with mCRC								
Sundemeyer et al. 2005 USA [28]	1993-2002	mCRC; adenocarcinoma	1020	106	10.4	8.6 - 12.4	Median 21 months	-
Holch et al. 2017 Germany [29]	2007-2014	mCRC, adenocarcinoma, received treatment	385	-	-	-	-	Until diagnosis of mCRC
Yeager et al. 2015 USA [30]	2008-2012	mCRC - genotyped tumors	918	130	14.2	12.1 -16.6	-	-
Kemeny et al 2014 USA [31]	2003-2[27] 013	mCRC – treated with liver resection, HAI and systemic chemotherapy. available KRAS data	169	-	KRAS WT 2 KRAS MUT 13.4	-	-	Median 44.3 months
Christensen et al. 2018 Denmark [32]	2005 - 2008	mCRC treated with cetuximab and irinotecan as third line treatment	480	65	13.5	10.7 - 16.9	-	Median 25.2 months

(*continued on next page*)

Table 1 (*continued*)

AuthorYearCountry	Years	Patients	No. CRC	No. BM	Incidence of BM (%)	95% CI (%)	Survival after BM diagnosis	Follow up
Register studies								
Kanthan et al. 1999 Canada [33]	1970-1995	All cases with CRC	5352	355	6.6	6 - 7.3	5-year survival: 16 – 38 %[b]	-
Riihimäki et al. 2016 Sweden [34]	2002-2012	All cases with CRC	49,096	1398	2.9	2.7 - 3.0	Median 5.5 months[c]	-
Qui et al. 2015 USA [35]	2010-2011	All cases with CRC, adenocarcinoma	46,027	356	0.8	0.7 - 0.9	1-year survival 36.2 %	Only at time of diagnosis of CRC
Van Gestel et al. 2014 Nederlands [36]	2003-2008	CRC; $T_{any}N_{any}M_0$ and underwent surgery	5671	157	3.0	2.4 - 3.2	-	Median 5.0 years – only sites at diagnosis of mCRC included.
Khattak et al. 2012 Australia [37]	2006-2011	mCRC – only single site metastases	1207	32	2.7	1.8 - 3.7	Median 5.1 months	-
Autopsy studies								
Hugen et al. 2014 Netherlands [38]	1991-2010	Autopsy, CRC	5817	103	1.7	-	-	-
Katoh et al. 1995 Japan [39]	1970-1987	Clinical and autopsy reports	118	28	23.7	16.4 - 32.4	-	-
Randomized study								
Heras 2007 Greece [40]	-	mCRC, BM	73	73	-	-	-	-

Abbreviations: BM = Bone metastases. CRC = colorectal cancer, mCRC = metastatic colorectal cancer, CC= colon cancer, RC= rectum cancer, T = tumor size, N = lymph node status, M = distant metastases, HAI = Hepatic artery chemo infusion.

[a] Only initial site of metastases.

[b] 5 year survival: BM and other metastases 16%, BM only 38%.

[c] Survival for patients with BM only.

risk of BM is inconclusive. Four studies of which three were conducted on selected cohorts, including one autopsy study, found no association [19,22,39]. However, a study by Santini et al. including 269 patients with BM found an association with poor differentiated tumors having the shortest time (6 months) to BM and well differentiated the longest (33 months). They did not include undifferentiated tumors in analysis [12]. The association between poorly differentiated tumor and BM are also observed in other tumor types e.g. gastric cancer has shown a relationship between poorly differentiated tumors and BM [42].

Signet-ring cell carcinoma seems to be associated with increased likelihood of BM though it is not well investigated. Whereas the other histological subtypes have not been found to affect likelihood of BM. Six studies performed a statistical analysis of the association between BM and histological types of CRC. The autopsy studies by Katoh et al. and Hugen et al. were the only two studies that performed separate analysis for signet-ring cell carcinoma compared to the other types. Both studies observed that signet-ring cell carcinoma showed a significantly higher incidence of BM than mucinous adenocarcinoma and adenocarcinoma [38,39].

The remaining four studies only compared adenocarcinoma to mucinous adenocarcinoma or adenocarcinoma to mucinous adenocarcinoma and signet ring carcinoma combined. None of the four found a significant association with risk of BM [12,16,22,34].

A hypothesis is that different molecular patterns of the cancer explain the pattern of metastases. Thus, genetic alterations in the tumor could possibly increase the ability of the tumor to seed certain organs such as the bone, brain or lung. *RAS* mutations are established predictors of poor response to anti-EGFR therapy and are associated with aggressive tumor biology [31,43,44]. *PIK3CA, BRAF*, and *RAS* mutations are the only mutations having been assessed for association with BM development. Only *RAS* mutations have been found to be a potential risk factor, though evidence is low and data conflicting.

Four studies have looked at whether *RAS* mutations (*KRAS* and *NRAS)* are associated with BM. All studies were conducted on selected and not comparable cohorts and the results were therefore hard to compare [18,30–32]. The study by Yaeger et al. was the largest of the four, and conducted on unselected mCRC patients as opposed to the three others. They identified a significant association on multivariable analysis between *RAS* mutation and BM with a hazard ratio (HR) of 1.62 (CI 95% = 1.1–2.3) [30]. However, *RAS* mutation status was used to guide anti-EGFR therapy which could be a potential confounder for the association between *RAS* and BM development [45]. Kemeny et al. only included *KRAS* exon 2 mutation but also identified a significantly higher cumulative incidence of BM among mutated compared to wild type in univariate analysis [31].

The two remaining studies did not find a significant association between *RAS* mutation and BM. However, one only included metastases at diagnosis of metastatic disease [18], and the other was conducted on a selected cohort of patients who all received the same third line treatment which might have confounded a potential association [32].

The association between *RAS* mutation and BM could be due to different gene expression and protein activations in cells with *RAS* mutation compared to *RAS* wildtype cells [45]. Another explanation could be changes in exosome composition. The exosome protein expression, including integrin expression, is markedly different between *RAS* wildtype and *RAS* mutant colon cancer cells [46], and studies have shown exosomal protein expression pattern to be important for organ-specific metastasis by directing creation of premetastatic niches [47]. Especially exosomal integrin was reported to have a crucial role in directing metastases to the bone [48].

3.2.4. Metastases at other sites

Having lymph node metastases at primary surgery and lung metastases at any time are identified as potential risk factors for developing BM. For liver metastases the results were inconclusive.

Having lymph node metastases at primary tumor surgery were statistically significant associated with increased risk of later development of BM in two studies, that both only included patients who

Table 2
Risk factors for bone metastases.

Author	Type of analysis[a]	Factors associated with increased risk of bone metastases	Other variable included in analysis but no association with bone metastases identified
Santini et al. [12]	Univariate Kaplan Meier estimate among (only including patients with BM)	Primary tumor grade (Poor grade).	Primary tumor site, Primary tumor stage, Primary tumor histology, Lymph node status, Use of adjuvant chemotherapy.
Zhenghong et al. [15]	Multivariate logistic regression	Rectal cancer, Lung metastases, CEA > 5μg/l.	Gender, Primary tumor histology, Primary tumor stage, Initial treatment, Liver metastases.
Li et al. [16]	Multivariate logistic regression	Rectal cancer, Lymph node met. at primary CRC surgery, Metachronous lung met.	Age, Gender, Primary tumor histology, Primary tumor stage, CA199.
Lan et al. [18]	Univariate Chi Square Test	None.	RAS mutation status, PIK3CA mutation status.
Sun et al. [19]	Multivariate logistic regression	Rectal cancer, Lymph node met. at primary CRC surgery.	Age, Gender, Albumin level, Hemoglobin, CEA, Transfusion, Primary tumor size, Primary tumor grade, Primary tumor stage, Primary tumor Invasion, Metastasis at diagnosis of CRC.
Liu et al. [22]	Univariate Chi Square test	Rectal cancer, Male.	Age, Primary tumor grade, Tumor histology.
Chiang et al. [25]	Univariate Kaplan Meier estimate	Middle and distal as opposed to proximal rectal cancer.	None.
Sundemeyer et al. [28]	Multivariate logistic regression	Rectal cancer, High number of systemic therapies, Lung metastases, Early stage disease, No liver metastases.	Peritoneal metastases, Adjuvant/neoadjuvant therapy.
Yeager et al. [30]	Univariate competing regression model[b]	Rectal cancer, RAS mutation, Lung metastases, Metastases at diagnosis of CRC.	Surgery.
Kemeny et al. [31]	Univariate cumulative incidence function	KRAS mutation.	None.
Christensen et al. [32]	Univariate cox regression	None.	Primary tumor location, Age, Gender, RAS mutation, BRAF mutation, PIK3CA mutation.
Riihimäki et al. [34]	Multivariate logistic regression	Rectal cancer. <u>- Colon cancer patients:</u> Male, Low age, Distal opposed to proximal colon. <u>- Rectal cancer patients:</u> Low age.	<u>- Colon cancer patients:</u> Tumor histology <u>- Rectal cancer patients:</u> Tumor histology, Gender
Qui et al. [35]	Univariate Chi Square test	Rectal cancer, Lung metastases, Liver metastases.	None.
Hugen et al. [38]	Univariate chi square test	Signet-ring cell carcinoma.	Primary tumor location.
Katoh et al. [39]	Univariate chi square and fisher exact test	Signet-ring cell carcinoma, Liver metastases, Lung metastases.	Primary tumor location, Primary tumor grade.

Abbreviations: CRC = Colorectal cancer, CEA = Carcinoembryonic antigen.
[a] If both univariate and multivariate analysis was performed, only multivariate analysis is presented.
[b] Multivariate analysis was performed but results of multivariate analysis only presented for RAS status where a positive association was identified.

underwent radical surgery [16,19]. Sun et al. identified an OR of 2.0 (CI 95% = 1.3–3.1) in multivariable analysis [19], and likewise Li et al. found a comparable OR of 2.3 (CI 95% = 1.3–4.1) [16]. Santini et al. found that patients who were lymph node positive at primary surgery had a median time to BM of only 13 months compared to 20 months among lymph node negative patients. However, the association was not statistically significant [12]. None of the above mentioned studies assessed whether lymph node involvement specifically increases the risk of BM or the association just reflects the association between lymph node status and increased risk of distant metastases. No studies have

looked at the effect on lymph node metastases developed after primary surgery.

Six studies (including one autopsy study, one register study, and three retrospective cohort studies) looked at the association between bone metastases and lung metastases and all found a significantly increased likelihood of BM [15,16,28,30,35,39]. Two of the retrospective cohort studies presented results of multivariable analysis and identified an OR of 2.5–4.8 of BM for patients having lung metastases [15,16]. The remaining studies only performed univariate analysis and found a 2–3 fold increase in incidence of BM among patients who had lung metastases compared to those who did not [28,30,35,39]. However, a causal relationship is hard to determine, since none of the studies demanded lung metastases to have been diagnosed before BM. Thus, several studies suggest that patients with rectal primaries are more likely than patients with colon primaries to present with lung metastases [49,50].

Four not comparable studies have looked at potential associations between liver metastases and BM with opposite results. Katoh et al. did in their autopsy study show a significantly increased prevalence of liver metastases among patients with BM compared to patients without BM [39]. Qui et al., who only included metastases at primary diagnosis, found a significant increased incidence of BM at diagnosis of CRC in patients who also had liver metastases compared to mCRC patients without liver metastases [35]. Oppositely, Sundemeyer et al. found a significant decreased incidence of BM among patients with liver metastases compared to patients without in a cohort of mCRC patients [28]. Lastly, univariate analysis revealed that liver metastases were not associated with BM in the study by Zhenghong et al. [15].

3.2.5. Gender

Male gender might be associated with increased risk of BM, although results are not conclusive. A large cohort study by Liu demonstrated a significantly higher incidence of BM among male CRC patients compared to female in univariate analysis [22]. Unfortunately, they did not adjust for location of primary tumor, which might bias the result. Male patients have increased incidence of rectum cancer compared to female patients [34], and the association between gender and BM might therefor be explained by this. More convincing, Riihimäki et al. demonstrated a significantly increased risk for BM for males compared to females among colon cancer patient in a large register study. This association remained significant when they adjusted for specific location in the colon. However, they did not find a significant association among rectal cancer patients [34]. Four smaller cohort studies, including a study conducted by our group, did not demonstrate any association [15,16,19,32].

This finding is in contrast with a recent review which concluded that for lung cancer females might have a more favorable bone microenvironment for metastasis formation [51]. Anyhow, the differences could possibly be the result of statistical variation.

3.2.6. Age of patients

Age might influence on the risk of developing BM, however, results are not conclusive. Low age (<60 years) was found to be associated with a significantly higher incidence of BM in the register study by Riihimäki et al. [34]. Among patients with colon cancer, patients older than 79 years had an odds ratio (OR) for developing BM of 0.4 (CI 95% = 0.3–0.6) compared to patients younger than 60 years. Among rectal cancer patients the OR was 0.3 (CI 95% = 0.2–0.4). Four smaller cohort studies did not find any association [16,19,22,32].

The young age could reflect a more aggressive disease in younger patients which leads to BM development [52] or it could be a consequence of older patients with several comorbidities did not receive treatment and, thus, had fewer evaluations and short OS [53].

3.2.7. Systemic therapies

The impact of systemic anticancer therapy on risk of BM among patients with CRC is not well investigated, and again firm conclusions cannot be drawn. Only the study by Sundemeyer et al. investigated the potential association between systemic therapies received in the metastatic setting and incidence of BM and found a significant association with high number of systemic therapies, as well as therapy with irinotecan and oxaliplatin compared to patients not receiving these therapies [28]. Two studies, including the one by Sundemeyer et al., looked at whether adjuvant/neoadjuvant therapy affected the likelihood of BM but neither found an association [12,28].

3.2.8. Survival

Survival after BM was mentioned in 16 studies. Median overall survival (OS) after diagnosis of BM ranged from 5 to 21 months (Table 1).

Median overall survival (OS) after diagnosis of BM ranged from 5 to 21 months (Table 1). However, due to the difference in time period patients received treatment and different cohorts, a direct comparison was difficult to make. In the studies that included all patients with CRC and BM the median OS after BM diagnoses ranged from 7 to 9.4 months [12–14]. The two register studies by Khattak et al. and Riihimäki et al. reported a median OS after diagnosis of metastatic disease in patients who only had BM. They found a median OS of 5.1 [37] and 5.5 months [34].

Several studies looked at the prognosis for patients with BM compared to patients with other metastases. The results in this regard are contradictory. The two register studies by Khattak et al. and Riihimäki et al. observed that mCRC patients with BM only, had significantly worse survival than patients with single site metastases at other sites such as liver and lung [34,37]. Likewise, Qui et al. did in their large register study find a 1 year cause specific survival of 29.6% for patients with BM only compared with 60.2% among patients with liver only and 36.2% among patients with lung only metastases [35]. Oppositely, three studies found a better prognosis for patients with BM only compared to patients with both BM and visceral metastases [14,22,33].

Five studies presented statistical analysis of factors associated with poor survival after diagnosis of BM. Summary of their results are found in Table 3. Several variables were associated with poor survival including: osteolytic lesions, more than one bone lesion, rib metastases, elevated CEA, other metastases, lung metastases and BM at diagnosis of CRC [12,17,20,22,35]. However, the studies were differently designed and used different cohorts making a comparison difficult. Furthermore, the studies all included different variables and only a few variables were included in analyses in more than one study. Therefore, the above mentioned results should be interpreted with caution, and new studies are needed to confirm a potential association.

3.3. Treatment

Eight studies described treatment of BM. Treatments used for BM included bisphosphonate therapy, systemic chemotherapy, radiotherapy, surgery and medical pain relief [12,14,19–22,40,54]. However, only three studies analyzed the effect of different treatments (bisphosphonate, radiotherapy and chemotherapy), including two retrospective cohort studies [12,22] and one small randomized study [40]. Summary of the three studies are presented in Table 4.

Bisphosphonate efficacy was statistically evaluated in all three studies [12,22,40]. The randomized study was a small pilot study and had several methodological short comings. Firstly, placebo treatment and randomization were not described. Secondly, no predefined protocol was described. Thirdly, no comparison of baseline characteristics was presented between treatment and placebo group and they did not perform any statistical adjustment for other factors which could have affected treatment outcome [40]. The incidence of adverse events was described as comparable to placebo but no analyses was presented [40]. The retrospective studies also had several shortcomings besides the retrospective nature of the study. In both studies patients received other

Table 3
Factors associated with poor survival after bone metastases diagnosis

Author	Type of analysis[a]	Factors associated with short survival after bone metastases	Other variable included in analysis but no association with survival after bone metastases
Santini et al. [12]	Univariate log-rank test	Osteolytic lesions, 2 or more bone lesions.	SRE, Bisphosphanate treatment.
Se-Jin Baek et al. [17]	Multivariable cox regression analysis	BoneM from colon cancer, Initial bone metastases.	SRE, Age, Gender, Body mass index.
Jimi et al. [20]	Multivariable cox regression analysis	Lung metastases, Rib metastases.	Site of primary cancer, Age, Gender, Liver metastases, Vertebral metastases, Pelvic metastases, CEA.
Liu et al. [22]	Multivariable cox regression analysis	Elevated CEA, Other metastases at BoneM diagnosis.	Tumor differentiation, Lymphatic metastasis, Perineural invasion, Alkaline fosfatase, Systemic chemotherapy, Radiotherapy, Bisphosfanate therapy.
Qui et al. [35]	Univariate log-rank test	None.	Lung metastases, Liver metastases.

Abbreviations: SRE = Skeletal related events, CEA = Carcinoembryonic antigen.
[a] If both univariate and multivariate analysis was performed, only multivariate analysis is presented.

therapies than bisphosphonate for bone metastases during study period, and neither study did statistically adjust for other factors [12,22].

Though the level of evidence is not high, the studies indicate that bisphosphonate treatment might improve outcome with regard to skeletal-related events (SRE) (defined as pathologic fracture, spinal cord compression, radiation therapy to bone, change in antineoplastic therapy and surgery to bone), but not overall survival. No study has evaluated denosumab in CRC.

This conclusion is consistent with studies on effect of antiresorptive treatment for BM in lung, breast and prostate cancer, where it has been shown to reduce skeletal related events (SRE) [7–10].

The effect of other therapies for BM from CRC is poorly investigated. Only the effect of systemic chemotherapy and radiotherapy has been analyzed with regard to OS after BM diagnosis, and this was only in one retrospective cohort study [22]. Systemic chemotherapy was found to improve survival among BM patients in univariate analysis. However, most patients also had visceral metastases and the improved survival might as well be related to the treatment effect on these, indicated by subgroup analyses of patients with BM as only metastatic site where no survival benefit was identified. Furthermore, no association was identified in multivariable survival analysis [22].

3.4. Limitations

This study had some limitations. First, we only had access to published material from the included studies. Second, in many of the included studies it was not possible to determine whether patients were consecutively included or not. This, in combination with many of the studies being retrospective, leads to a risk of publication bias. Most of the present studies contained few BM patients, and did not have sufficient strength or the right study design to clarify which factors increase the risk of BM, or which factors are prognostic. Furthermore, the literature and quality of studies regarding efficacy treatment for BM from CRC are sparse, making recommendation in this regard unreliable. This review highlight the need for new studies about BM. Especially regarding treatment for BM from CRC.

4. Conclusion

The literature written about BM from CRC is sparse and heterogeneously designed studies make firm conclusion difficult. BM in patients with CRC are relatively uncommon disease manifestation, which occurs in 3–7%. It was not possible to detect an increase in incidence of BM from CRC and study heterogeneity made conclusions uncertain. The most well established risk factors for BM are rectal cancer, having lymph node invasion at surgery of primary tumor, and lung metastases at any time. Other risk factors have been suggested but results are not conclusive. Survival ranges from 5 to 21 months after diagnosis of BM in included studies depending on cohort. Several variables have been suggested as potential prognostic markers but are all poorly investigated. Treatments of BM are not well investigated though patients seem to benefit from bisphosphanate treatment with regard to lower risk of skeletal related events.

Table 4
Treatment of bone metastases

Author	End point regarding treatment efficacy	Treatment of BoneM and comparison (patients in group)	Results
Santini et al. [12]	Time to first SRE, OS.	Zoledronic acid (126) vs no bisphosphonate therapy (31)	Time to first SRE: Significantly longer time for Zolodronic acid vs no bisphosphonate therapy (2 months vs1 months, $p = 0.009$). OS: NS.
Liu et al. [22]	OS.	Bisphosphonate (108) vs. no bisphosphonate (134), Radiation therapy (172) vs no radiation therapy (70), Chemotherapy (171) vs no chemotherapy (71), Combination therapy (192) vs single therapy (38).	Univariate analysis Bisphosphonate treatment: NS, Radiation therapy: NS, Chemotherapy: Significantly ($p = 0.012$) associated with better OS[a], Combination therapy: Significantly (p = 0.01) associated with better OS[a] Multivariate analysis Chemotherapy: NS.
Heras et al. [40]	Primary endpoint: Proportion with SRE. Secondary endpoint: time to SRE, events per year, time to progression of bone lesion.	Ibandronate treatment vs placebo.	Ibandronate significantly superior to placebo regarding: Proportion with SRE (39 % vs. 78 %, $p = 0.019$), Time to first SRE (214 days vs 81 days, p = 0.009), SRE per year (2.36 vs 3.14, $p = 0.018$), Time to progression of bone lesion (214 days vs 81 days, $p = 0.018$).

Abbreviations: SRE = Skeletal related events, defined as pathologic fracture, spinal cord compression, radiation therapy to bone, change in antineoplastic therapy and surgery to bone, OS = Overall survival, NS = No significant association, BM = Bone metastases.
[a] Effect size not reported.

This review highlight the need for new studies about BM from CRC.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of interest

The authors report no conflicts of interest.

References

[1] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, CA Cancer J. Clin. 65 (2) (2015) 87–108.
[2] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2015, CA Cancer J. Clin. 65 (1) (2015) 5–29.
[3] D.L. Nielsen, J.A. Palshof, F.O. Larsen, B.V. Jensen, P. Pfeiffer, A systematic review of salvage therapy to patients with metastatic colorectal cancer previously treated with fluorouracil, oxaliplatin and irinotecan ± targeted therapy, Cancer Treat Rev. 40 (6) (2014) 701–715.
[4] K.M. Augestad, P.M. Bakaki, J. Rose, B.P. Crawshaw, R.O. Lindsetmo, L.M. Dorum, S.M. Koroukian, C.P. Delaney, Metastatic spread pattern after curative colorectal cancer surgery. A retrospective, longitudinal analysis, Cancer Epidemiol 39 (5) (2015) 734–744.
[5] R. von Moos, C. Sternberg, J.J. Body, C. Bokemeyer, Reducing the burden of bone metastases: current concepts and treatment options, Support Care Cancer 21 (6) (2013) 1773–1783.
[6] C. Kamby, The pattern of metastases in human breast cancer: methodological aspects and influence of prognostic factors, Cancer Treat Rev. 17 (1) (1990) 37–61.
[7] C. Kamby, S. Tarp, A. Mellemgaard, R. Christensen, S. Cold, P. Eiken, E.H. Jakobsen, N.C. Langkilde, S.T. Langkjer, T. Laursen, S.S. Ottesen, A.G. Pedersen, L.E. Stenbygaard, P.M. Vestlev, Prevention of skeletal related events in patients with bone metastases from solid tumours. Ugeskr Laeger 176 (8A) (2014) 645–648.
[8] N. Junker, D.L. Nielsen, C. Kamby, Biphosphonates in breast cancer–based on a cochrane meta-analysis, Ugeskr Laeger 169 (37) (2007) 3108–3111.
[9] M.H. Wong, M.R. Stockler, N. Pavlakis, Bisphosphonates and other bone agents for breast cancer, Cochrane Database Syst. Rev. 2 (2012) CD003474.
[10] L.S. Rosen, D.H. Gordon, W. Dugan, P. Major Jr., P.D. Eisenberg, L. Provencher, M. Kaminski, J. Simeone, J. Seaman, B.L. Chen, R.E. Coleman, Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion, Cancer 100 (1) (2004) 36–43.
[11] R. Siegel, C. Desantis, A. Jemal, Colorectal cancer statistics, 2014, CA Cancer J. Clin. 64 (2) (2014) 104–117.
[12] D. Santini, M. Tampellini, B. Vincenzi, T. Ibrahim, C. Ortega, V. Virzi, N. Silvestris, R. Berardi, C. Masini, N. Calipari, D. Ottaviani, V. Catalano, G. Badalamenti, R. Giannicola, F. Fabbri, O. Venditti, M.E. Fratto, C. Mazzara, T.P. Latiano, F. Bertolini, F. Petrelli, A. Ottone, C. Caroti, L. Salvatore, A. Falcone, P. Giordani, R. Addeo, M. Aglietta, S. Cascinu, S. Barni, E. Maiello, G. Tonini, Natural history of bone metastasis in colorectal cancer: final results of a large Italian bone metastases study, Ann Oncol 23 (8) (2012) 2072–2077.
[13] F. Portales, S. Thezenas, E. Samalin, E. Assenat, T. Mazard, M. Ychou, Bone metastases in gastrointestinal cancer, Clin. Exp. Metastasis 32 (1) (2015) 7–14.
[14] D.C. Bonnheim, N.J. Petrelli, L. Herrera, D. Walsh, A. Mittelman, Osseous metastases from colorectal carcinoma, Am. J. Surg. 151 (4) (1986) 457–459.
[15] Z.Z. Zhenghong, Z. Guoweijian, Y.X. Caiyunyun, Retrospective study of predictors of bone metastasis in colorectal cancer patients, J, Bone Oncol. 9 (2017) 25–28.
[16] A. Li, L. Kasmann, D. Rades, C. Fu, A Scoring system to predict the development of bone metastasis after radical resection of colorectal cancer, Anticancer Res. 37 (9) (2017) 5169–5172.
[17] S.J. Baek, H. Hur, B.S. Min, S.H. Baik, K.Y. Lee, N.K. Kim, The characteristics of bone metastasis in patients with colorectal cancer: a long-term report from a single institution, World J. Surg. 40 (4) (2016) 982–986.
[18] Y.T. Lan, L. Jen-Kou, C.H. Lin, S.H. Yang, C.C. Lin, H.S. Wang, W.S. Chen, T.C. Lin, J.K. Jiang, S.C. Chang, Mutations in the RAS and PI3K pathways are associated with metastatic location in colorectal cancers, J. Surg. Oncol. 111 (7) (2015) 905–910.
[19] C. Sun, Y. Deng, H. Zhou, Z.Q. Hu, Risk factors for the development of metachronous bone metastasis in colorectal cancer patients after curative resection, Int. J. Surg. 21 (2015) 145–149.
[20] S. Jimi, T. Yasui, M. Hotokezaka, K. Shimada, Y. Shinagawa, H. Shiozaki, N. Tsutsumi, S. Takeda, Clinical features and prognostic factors of bone metastases from colorectal cancer, Surg. Today 43 (7) (2013) 751–756.
[21] M. Nozue, Y. Oshiro, M. Kurata, K. Seino, N. Koike, T. Kawamoto, H. Taniguchi, T. Todoroki, K. Fukao, Treatment and prognosis in colorectal cancer patients with bone metastasis, Oncol. Rep. 9 (1) (2002) 109–112.
[22] F. Liu, J. Zhao, J. Xie, L. Xie, J. Zhu, S. Cai, H. Zheng, Y. Xu, Prognostic risk factors in patients with bone metastasis from colorectal cancer, Tumour Biol. (2016).
[23] E.S. Roth, D.T. Fetzer, B.J. Barron, U.A. Joseph, I.W. Gayed, D.Q. Wan, Does colon cancer ever metastasize to bone first? A temporal analysis of colorectal cancer progression, BMC Cancer 9 (2009) 274.
[24] R. Amri, L.G. Bordeianou, P. Sylla, D.L. Berger, Variations in metastasis site by primary location in colon cancer, J. Gastrointest. Surg. 19 (8) (2015) 1522–1527.
[25] J.M. Chiang, P.S. Hsieh, J.S. Chen, R. Tang, J.F. You, C.Y. Yeh, Rectal cancer level significantly affects rates and patterns of distant metastases among rectal cancer patients post curative-intent surgery without neoadjuvant therapy, World J. Surg. Oncol. 12 (2014) 197.
[26] V. Patanaphan, O.M. Salazar, Colorectal cancer: metastatic patterns and prognosis, South. Med. J. 86 (1) (1993) 38–41.
[27] S. Besbeas, M.W. Stearns Jr., Osseous metastases from carcinomas of the colon and rectum, Dis. Colon Rectum 21 (4) (1978) 266–268.
[28] M.L. Sundermeyer, N.J. Meropol, A. Rogatko, H. Wang, S.J. Cohen, Changing patterns of bone and brain metastases in patients with colorectal cancer, Clin. Colorectal Cancer 5 (2) (2005) 108–113.
[29] J.W. Holch, M. Demmer, C. Lamersdorf, M. Michl, C. Schulz, J.C. von Einem, D.P. Modest, V. Heinemann, Pattern and dynamics of distant metastases in metastatic colorectal cancer, Visceral Med. 33 (1) (2017) 70–75.
[30] R. Yaeger, E. Cowell, J.F. Chou, A.N. Gewirtz, L. Borsu, E. Vakiani, D.B. Solit, N. Rosen, M. Capanu, M. Ladanyi, N. Kemeny, RAS mutations affect pattern of metastatic spread and increase propensity for brain metastasis in colorectal cancer, Cancer 121 (8) (2015) 1195–1203.
[31] N.E. Kemeny, J.F. Chou, M. Capanu, A.N. Gewirtz, A. Cercek, T.P. Kingham, W.R. Jarnagin, Y.C. Fong, R.P. DeMatteo, P.J. Allen, J. Shia, C. Ang, E. Vakiani, M.I. D'Angelica, KRAS mutation influences recurrence patterns in patients undergoing hepatic resection of colorectal metastases, Cancer 120 (24) (2014) 3965–3971.
[32] T.D. Christensen, J.A. Palshof, F.O. Larsen, T.S. Poulsen, E. Hogdall, P. Pfeiffer, B.V. Jensen, M.K. Yilmaz, D. Nielsen, Associations between primary tumor RAS, BRAF and PIK3CA mutation status and metastatic site in patients with chemo-resistant metastatic colorectal cancer, Acta oncologica (Stockholm, Sweden) 57 (8) (2018) 1–6.
[33] R. Kanthan, J. Loewy, S.C. Kanthan, Skeletal metastases in colorectal carcinomas: a Saskatchewan profile, Dis. Colon Rectum 42 (12) (1999) 1592–1597.
[34] M. Riihimaki, A. Hemminki, J. Sundquist, K. Hemminki, Patterns of metastasis in colon and rectal cancer, Sci. Rep. 6 (2016) 29765.
[35] M. Qiu, J. Hu, D. Yang, D.P. Cosgrove, R. Xu, Pattern of distant metastases in colorectal cancer: a SEER based study, Oncotarget 6 (36) (2015) 38658–38666.
[36] Y.R. van Gestel, I.H. de Hingh, M.P. van Herk-Sukel, F.N. van Erning, L.V. Beerepoot, J.H. Wijsman, G.D. Slooter, H.J. Rutten, G.J. Creemers, V.E. Lemmens, Patterns of metachronous metastases after curative treatment of colorectal cancer, Cancer Epidemiol. 38 (4) (2014) 448–454.
[37] M.A. Khattak, H.L. Martin, C. Beeke, T. Price, S. Carruthers, S. Kim, R. Padbury, C.S. Karapetis, Survival differences in patients with metastatic colorectal cancer and with single site metastatic disease at initial presentation: results from South Australian clinical registry for advanced colorectal cancer, Clin. Colorectal Cancer 11 (4) (2012) 247–254.
[38] N. Hugen, C.J. van de Velde, J.H. de Wilt, I.D. Nagtegaal, Metastatic pattern in colorectal cancer is strongly influenced by histological subtype, Ann. Oncol. 25 (3) (2014) 651–657.
[39] M. Katoh, M. Unakami, M. Hara, S. Fukuchi, Bone metastasis from colorectal cancer in autopsy cases, J. Gastroenterol. 30 (5) (1995) 615–618.
[40] P. Heras, S. Karagiannis, K. Kritikos, A. Hatzopoulos, D. Mitsibounas, Ibandronate is effective in preventing skeletal events in patients with bone metastases from colorectal cancer, Eur. J. Cancer Care (Engl) 16 (6) (2007) 539–542.
[41] M. Vider, Y. Maruyama, R. Narvaez, Significance of the vertebral venous (Batson's) plexus in metastatic spread in colorectal carcinoma, Cancer 40 (1) (1977) 67–71.
[42] F.P. Turkoz, M. Solak, S. Kilickap, A. Ulas, O. Esbah, B. Oksuzoglu, S. Yalcin, Bone metastasis from gastric cancer: the incidence, clinicopathological features, and influence on survival, J. Gastric Cancer 14 (3) (2014) 164–172.
[43] J.R. Hecht, J.Y. Douillard, L. Schwartzberg, A. Grothey, S. Kopetz, A. Rong, K.S. Oliner, R. Sidhu, Extended RAS analysis for anti-epidermal growth factor therapy in patients with metastatic colorectal cancer, Cancer Treat Rev. 41 (8) (2015) 653–659.
[44] J.N. Vauthey, G. Zimmitti, S.E. Kopetz, J. Shindoh, S.S. Chen, A. Andreou, S.A. Curley, T.A. Aloia, D.M. Maru, RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases, Ann. Surg. 258 (4) (2013) 619–626 discussion 626-7.
[45] R. Yaeger, E. Cowell, J.F. Chou, A.N. Gewirtz, L. Borsu, E. Vakiani, D.B. Solit, N. Rosen, M. Capanu, M. Ladanyi, N. Kemeny, RAS mutations affect pattern of metastatic spread and increase propensity for brain metastasis in colorectal cancer, Cancer (2014).
[46] M. Demory Beckler, J.N. Higginbotham, J.L. Franklin, A.J. Ham, P.J. Halvey, I.E. Imasuen, C. Whitwell, M. Li, D.C. Liebler, R.J. Coffey, Proteomic analysis of exosomes from mutant KRAS colon cancer cells identifies intercellular transfer of mutant KRAS, Mol. Cell Proteomics 12 (2) (2013) 343–355.
[47] A. Hoshino, B. Costa-Silva, T.L. Shen, G. Rodrigues, A. Hashimoto, M. Tesic Mark, H. Molina, S. Kohsaka, A. Di Giannatale, S. Ceder, S. Singh, C. Williams, N. Soplop, K. Uryu, L. Pharmer, T. King, L. Bojmar, A.E. Davies, Y. Ararso, T. Zhang, H. Zhang, J. Hernandez, J.M. Weiss, V.D. Dumont-Cole, K. Kramer, L.H. Wexler, A. Narendran, G.K. Schwartz, J.H. Healey, P. Sandstrom, K.J. Labori, E.H. Kure, P.M. Grandgenett, M.A. Hollingsworth, M. de Sousa, S. Kaur, M. Jain, K. Mallya, S.K. Batra, W.R. Jarnagin, M.S. Brady, O. Fodstad, V. Muller, K. Pantel, A.J. Minn, M.J. Bissell, B.A. Garcia, Y. Kang, V.K. Rajasekhar, C.M. Ghajar, I. Matei, H. Peinado, J. Bromberg, D. Lyden, Tumour exosome integrins determine organotropic metastasis, Nature 527 (7578) (2015) 329–335.
[48] J.G. Schneider, S.R. Amend, K.N. Weilbaecher, Integrins and bone metastasis: integrating tumor cell and stromal cell interactions, Bone 48 (1) (2011) 54–65.
[49] J.R. Robinson, P.A. Newcomb, S. Hardikar, S.A. Cohen, A.I. Phipps, Stage IV

colorectal cancer primary site and patterns of distant metastasis, Cancer epidemiology 48 (2017) 92–95.
[50] H.D. Pan, G. Zhao, Q. An, G. Xiao, Pulmonary metastasis in rectal cancer: a retrospective study of clinicopathological characteristics of 404 patients in Chinese cohort, BMJ Open 8 (2) (2018) e019614.
[51] M.C. Farach-Carson, S.H. Lin, T. Nalty, R.L. Satcher, Sex differences and bone metastases of breast, lung, and prostate cancers: do bone homing cancers favor feminized bone marrow? Front. Oncol. 7 (2017) 163.
[52] J.B. O'Connell, M.A. Maggard, E.H. Livingston, C.K. Yo, Colorectal cancer in the young, Am. J. Surg. 187 (3) (2004) 343–348.
[53] K.W. Hoeben, L.N. van Steenbergen, A.J. van de Wouw, H.J. Rutten, D.J. van Spronsen, M.L. Janssen-Heijnen, Treatment and complications in elderly stage III colon cancer patients in the Netherlands, Ann. Oncol. 24 (4) (2013) 974–979.
[54] J.Y. Baek, M.H. Kang, Y.S. Hong, T.W. Kim, D.Y. Kim, J.H. Oh, S.H. Lee, J.H. Park, J.H. Kim, S.Y. Kim, Characteristics and prognosis of patients with colorectal cancer-associated brain metastases in the era of modern systemic chemotherapy, J. neuro-oncol. 104 (3) (2011) 745–753.